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Award Number: DAMD17-00-1-0033

TITLE: Locating a Prostate Cancer Susceptibility Gene on the X
Chromosome by Linkage Disequilibrium Mapping Using Three
Founder Populations in Quebec and Switzerland

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REPORT DATE: March 2001

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

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REPORT DOCUMENTATION PAGE			Form Approved OMB No. 074-0188	
Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302, and to the Office of Management and Budget, Paperwork Reduction Project (0704-0188), Washington, DC 20503				
1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE March 2001	3. REPORT TYPE AND DATES COVERED Annual (1 Mar 00 - 28 FEB 01)		
4. TITLE AND SUBTITLE Locating a Prostate Cancer Susceptibility Gene on the X Chromosome by Linkage Disequilibrium Mapping Using Three Founder Populations in Quebec and Switzerland		5. FUNDING NUMBERS DAMD17-00-1-0033		
6. AUTHOR(S) William D. Foulkes, M.B., Ph.D.				
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) McGill University Montreal Quebec Canada H3A 2T5 E-Mail: mdwf@musica.mcgill.ca		8. PERFORMING ORGANIZATION REPORT NUMBER		
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012		10. SPONSORING / MONITORING AGENCY REPORT NUMBER		
11. SUPPLEMENTARY NOTES				
12a. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited			12b. DISTRIBUTION CODE	
13. ABSTRACT (Maximum 200 Words) The funded proposal has not yet been activated. We have obtained DOD-endorsed ethical approval at McGill University, but because we are waiting for ethical approval at the other 2 sites we cannot begin. The need to obtain ethical approval at all sites within the McGill University Hospitals system led to much longer delays than anticipated as four separate ethics board had to approve the DOD-endorsed documents. This endeavour took from September 1999 to October 2000. We now have approval at McGill University and at all the component hospital sites. The work required to obtain IRB approval in Switzerland was substantially more complicated than we had envisioned as their system is very different from ours in North America. We have submitted the Single Project Assurance package from Switzerland and are currently waiting to hear from the DOD. We have submitted parts 2,3 and 4 of the Chicoutimi (Quebec) SPA and the ethics committee have met and approval should be forthcoming in the next month or so. We waited for McGill IRB approval before involving Chicoutimi because we wanted to provide them with DOD-approved documents in French so that they wouldn't have to repeat our work. Realistically, we anticipate that within 6 months, approval will have been obtained at all sites and the study will be ready to begin.				
14. SUBJECT TERMS			15. NUMBER OF PAGES 10	
			16. PRICE CODE	
17. SECURITY CLASSIFICATION OF REPORT Unclassified	18. SECURITY CLASSIFICATION OF THIS PAGE Unclassified	19. SECURITY CLASSIFICATION OF ABSTRACT Unclassified	20. LIMITATION OF ABSTRACT Unlimited	

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Locating a prostate cancer susceptibility gene on the X chromosome by linkage disequilibrium mapping using three founder populations in Quebec and Switzerland

William D Foulkes

New Investigator Award: DAMD17-00-1-0033

Introduction

In this study, we are funded to precisely localise a prostate cancer susceptibility gene to the X chromosome (Xq) by linkage disequilibrium mapping. We plan to use three founder populations: 1) the French Canadian inhabitants of the Saguenay-Lac St Jean region of Quebec; 2) the Ashkenazi Jewish population of greater Montreal; 3) the population of the Swiss Canton of Valais. We have chosen these three populations because they have all been shown to contain founder mutations in various disease-associated genes and because they are accessible to us and have participated in research studies in the past.

Body of text

Task 1: Case ascertainment, contact, consent, interview, DNA extraction and pathology confirmation, years 1-3 (aim to complete in second quarter of year 3).

- Obtain approval for this study from relevant IRBs

In progress

The goals established for all other items in Task 1 (listed below) have NOT been achieved because we have not obtained ethical approval at all sites, and human subject research cannot commence until approval has been granted at all sites. Please see the appendix for a full description of the how we have been working towards achieving this first goal of Task 1.

- Identify all prevalent cases of prostate cancer at hospitals serving the three populations under study: Chicoutimi, McGill University Hospitals (Quebec) and Sion and affiliated regional hospitals, Valais, Switzerland. This will be carried out by contacting medical records, out-

patient charts and cancer registries, confirming that the patient is living and then seeking permission from treating physicians (some of whom are collaborators on this proposal) to contact their patients by letter

- Identify incident cases through urology clinics at the three centres (Chicotimi, McGill University, Sion). Method of contact as for prevalent cases. Contact relatives via case.
- Consent all eligible participants (case n~640)
- Interview and construct three-generation pedigree for each case and control
- Show Ishihara charts to cases
- Draw blood from all consenting participants
- Extract DNA locally at each participating centre, transfer aliquots of DNA to PI laboratory for quality check and storage
- Transfer representative slides and blocks to Montreal for central pathology review (NB this will take place after ascertainment as we expect few cases will be re-classified and subsequently excluded)
- Create central database at the MGHRI

Key Research Accomplishments

- Nil

Reportable outcomes

1. Published work

We have not published any work directly related to this project for reasons that are clear from the text above. However, we have continued to work in prostate cancer genetics. I have listed here the most relevant work to which I have contributed March 1, 2000 - February 28, 2001.

Xu JF and International Consortium for Prostate Cancer Genetics (ICPCG). Combined Analysis of Hereditary Prostate Cancer Linkage to *1q24-25*: Results from 772 Hereditary Prostate Cancer Families from the International Consortium for Prostate Cancer Genetics. *Am J Hum Genet* **66**: 945-957, 2000 (WDF was a member of the ICPCG writing committee for this paper).

Singh R, Eeles RA, Durocher F, Simard J, Edwards S, Badzioch, Kote-Jarai Z, Teare D, Ford D, Dearnley D, Arden-Jones A, Murkin A, Dowe A, Shearer R, Kelly J, The CRC/BPG UK Familial Prostate Cancer Study Collaborators, Labrie F, Easton DF, Narod SA, Tonin PN and Foulkes WD. High risk genes predisposing to prostate cancer development: do they exist? *Prostate Cancer and Prostate Diseases* **3**, 241-247, 2000.

Badzioch, M, Eeles R, Leblanc G, Foulkes WD, Giles G, Edwards S, Goldgar DE, Hopper J, Bishop DT, Moller P, Heimdal K, Easton D, the CRC/BPG UK Familial Prostate Cancer Study Group, the EU Biomed Collaborators and Simard J. Suggestive evidence for a site-specific prostate cancer gene on chromosome 1p36. *J Med Genet* **37**: 947-949, 2000.

Conclusions

At the present time, we do not have any scientific data to report. We have not used the funds allocated for this grant for any purpose other than arranging for ethical approval at all sites and other related office costs. We hope very much that we will be able to report in the next statement of work that Task 1 is well underway.

Appendix 1

Log of contact between Principal Investigator and Ethics Committees at all sites, and with Angela D. Howard, Ph.D., AMDEX, Corp. USAMRMC-Regulatory, Compliance and Quality (RCQ) Human Subjects Protection Specialist

Abbreviations:

DOD-Department of Defence
IRB-Institutional Review Board
JGH-Sir M.B. Davis-Jewish General Hospital
MGH-Montreal General Hospital
MGHRI-Montreal General Hospital Research Institute
McGill-McGill University
MUHC-McGill University Health Centre
RVH-Royal Victoria Hospital

Letter of funding received Sept 1999.

MGH IRB submission in fall 1999

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JGH IRB submission September 27, 1999

↓

MGHRI Safety Program Plan and Certificate of Environmental Compliance for Dr. William Foulkes' laboratory sent to DOD October 1999

↓

Changes requested by JGH IRB in letter of October 20, 1999

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Re-submitted changed documents to JGH IRB on November 12, 1999

↓

Minor changes requested by JGH IRB

↓

Re-submitted minor changes on December 15, 1999 to JGH IRB

↓

JGH IRB approval received on January 6, 2000

↓

After receipt of additional information received by the DOD regarding the need to be covered by a multiple project assurance (MPA), and upon finding out that McGill is the only university in Canada with an MPA, the study submitted to McGill IRB for January 4, 2000 deadline

Submitted

- protocol
- consent form for cases
- consent form for controls
- intake sheets for cases and controls
- tissue donation form
- Army Optional Form 310

↓

McGill IRB January 25, 2000

Protocol approved, changes requested to consent forms

↓

Re-submitted consents forms dated January 28, 2000

↓

McGill IRB approved study February 17, 2000. Protocol stamped February 17, 2000, consent forms for cases and controls, stamped February 17, 2000; donation form, stamped February 17, 2000; intake sheets, stamped February 17, 2000, optional form 310, completed and signed, dated February 17th, 2000

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Submitted McGill approved documents to the IRBs of the JGH, MUHC-MGH and MUHC-RVH on March 1, 2000

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Sent letter to McGill IRB on March 17, 2000 regarding 2 sentences to be added to control consent form (omitted by error), control consent dated March 17, 2000

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Chicoutimi SPA parts 2, 3, 4 sent to Army April 2000

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April 11th 2000, letter from JGH IRB informed us that they had serious ethical and legal concerns regarding the wording of the donation form

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McGill IRB letter April 18, 2000

control consent of March 17, 2000 approved

↓

April, 2000. McGill IRB approval revoked following conversations between the JGH IRB and McGill IRB lawyers regarding donation form

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April-June 2000: discussion with JGH IRB, McGill IRB, Army in order to solve problem of wording of tissue donation form

↓

Submitted revised protocol (dated June 1, 2000) consent forms (dated June 1, 2000) and tissue donation form (dated June 1, 2000) to McGill IRB on June 14, 2000

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McGill IRB approved revisions and reinstated approval for study in letter of June 20, 2000

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Request by DOD in e-mail dated June 26, 2000 for changes to McGill approved documents (protocol, consents) and request to draw up doctor and case letters

↓

Replied to the DOD by letter dated July 3, 2000 with:

- basic protocol dated July 3, 2000
- letters to doctor and patients
- consent forms dated June 28, 2000

↓

MGHRI Safety Program Plan and Certificate of Environmental Compliance for Dr. Thomas Hudson's laboratory sent to DOD June 2000

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Swiss Safety Program Plan and Certificate of Environmental Compliance sent to Army June 2000

↓

DOD responded August 2, 2000 wanting minor changes to consent forms

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Revisions made and consent forms emailed August 2, 2000 (forms dated August 2, 2000)

↓

DOD approval complete for all documents via email of August 7th, 2000

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Revised documents submitted to McGill IRB August 9, 2000 case and control consent forms dated August 2, 2000 letter to doctor and cases

↓

McGill IRB letter dated September 26, 2000

- consents (2) August 2, 2000 version approved
- letters doctor and cases approved (they dated these documents August 2, 2000)

↓

Study re-submitted to the JGH IRB, MUHC-MGH IRB, and MUHC-RVH on October 2, 2000

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Study approved at MUHC-RVH on October 12, 2000

Study approved at MUHC-MGH on October 23, 2000

Study approved at JGH on October 23, 2000

↓

We found out information regarding the MPA in another context, and a letter was faxed November 1, 2000 to McGill IRB re: clarification about whether MPA covers MGH and/or MGHRI (institution where funds were to be administered from)

↓

McGill IRB informed us by phone that in order to be covered by the MPA, the funds must be administered by McGill. Otherwise, if the funds are to be administered at the MGHRI, we must go back and apply for SPAs to cover each institution.

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Conversations ensued between the grants offices at the MGHRI, McGill University and the DOD, and a request package for the opening of an account at McGill was submitted on November 23, 2000.

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Hard copies of McGill IRB, MUHC-MGH IRB, MUHC-RVH IRB, and JGH IRB approved documents sent to Army on November 23, 2000

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French translation of approved McGill documents sent to Army December 2000

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Account opened at McGill, paperwork with Army rectified via an Assistance Agreement dated January 24, 2001

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Swiss SPA documents mailed to Army on February 22, 2001